REMARKS

The claims are 3 to 7.

The present invention relates to a modified-release pharmaceutical composition for administering an effective amount of efletirizine in order to obtain both rapidly an effective plasma concentration and also maintenance of a minimum effective concentration over a prolonged period. For that purpose, the modified-release composition comprises at least two fractions containing the active principle. The first fraction allows immediate release of the active principle and the second allows prolonged release of the active principle and the maintenance of an effective plasma concentration over a prolonged period. The compositions obtained are particularly suitable for administration in a single daily dose.

Efletirizine cannot be compared to various antihistamines, such as loratadine and cetirizine, due to its very specific pharmacokinetic characteristics (and in particular half life time, plasmatic elimination, oral clearance). Kreutner discloses all three as equivalent for his purposes.

Thus, for example, loratadine is a long acting drug, it exhibits a dose-related inhibition of the histamine-induced skin wheal and flare response in humans which is rapid in onset, is apparent at 2 hours and persists throughout the 24 hour observation period. The loratadine elimination half-life (t 1/2b) ranged from 7.8 to 11 hours; for descarboethoxyloratadine, its t 1/2b ranged from 17 to 24 hours; for cetirizine it ranges from 6.5 to 10. So due to their pharmacokinetic characteristics, these antihistamines act naturally over one day and it is not absolutely necessary to add specific excipients for obtaining a single daily dose tablet.

On the contrary, the half-life t ½b of efletirizine ranges only from 2.5 to 3.5, and hence, efletirizine does not persist throughout the 24-hour observation period. Consequently, a very specific pharmaceutical composition is absolutely required in order to obtain a single daily dose tablet.

Moreover, due to the various pharmacokinetic characteristics, a galenic composition containing loratadine as active ingredient will not at all lead to the same results with efletirizine as active ingredient in place.

The composition of the invention can be administered orally and it is possible to control the release of the efletirizine in such a way that it may be administered in a single daily dose while at the same time exhibiting a rapid therapeutic activity. The bioavailability has been modified by means of a prolonged-release formulation which releases the active principle gradually over the entire length of the gastrointestinal tract, over a longer period of time, and thus avoids repeated absorption of a pharmaceutical composition by the patient.

It has been established that prolonged-release pharmaceutical formulations commonly used by those skilled in the art and applied to efletirizine have the disadvantage of reaching the effective plasma concentration later and therefore of delaying the therapeutic action of the active principle. In addition, it has been noted that such prolonged-release formulations, compared to the administration of two immediate-release doses 12 hours apart, induce a decrease in the maximum plasma concentration of efletirizine and also a decrease in its bioavailability.

In fact, the various studies carried out have also revealed that efletirizine exhibits better absorption in the upper portions of the gastrointestinal tract.

With the composition of the present invention, it is possible, in order to relieve the patients as quickly as possible, to rapidly provide them with a therapeutically effective dose of efletirizine while at the same time maintaining an effective minimum concentration for as long as possible, and preferably around 24 hours.

In addition, all of these conditions must be met while maintaining the bioequivalence with two administrations of 5 to 25 mg of efletirizine in an immediate-release form, given 12 hours apart.

The novel compositions of the invention have also shown, particularly surprisingly, that by combining at least one immediate-release fraction and at least one prolonged-release fraction, the pharmaceutical compositions thus obtained make it possible to reduce, in a more or less substantial manner, according to the distribution of the active principle between the fractions, the

influence of having a meal before their absorption by the patient, this effect absolutely not being observed for immediate-release compositions. This unexpected discovery is particularly useful for maintaining the bioequivalence and the maximum plasma concentration of a pharmaceutical composition, whether it is taken before or after the meal, and, as a result, the consequences of incorrect handling or use by the patient are reduced.

For the foregoing reasons, it is apparent that the rejections on prior art are untenable and should be withdrawn.

No further issues remaining, allowance of this application is respectfully requested.

Respectfully submitted,

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